Remarks

In response to the Examiner's previous restriction requirements and the Applicant's election of claims 1 and 6-8 in Group II, the Applicant has canceled claims 2-5 and 9-12.

The Examiner objected to claim 1 because of an informality and suggested that the Applicant delete the words "is of a" and "number". In response, the Applicant has amended claim 1, in part, to address the Examiner's objection.

The Examiner rejected claims 1 and 6-8 under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner stated that, while being enabling for determining the amount of estradiol bound to huntintin protein *in vitro*, the specification does not reasonably provide enablement for inhibiting the development of Huntington's disease, or for determining the rate of binding estradiol to huntintin, or for determining trinucleotide repeat patterns in any nucleic acid, or for administering sufficient amounts of a compound to an individual. In summary, the Examiner stated that the specification does not enable someone skilled in the art to make and use the invention commensurate in scope with the claims.

In response, the Applicant has, in part, amended claim 1 and, in part, respectfully traverses part of the Examiner's grounds for rejection. It is known by those skilled in the art that when the huntingtin polyglutamine protein is bound up, development and progression of Huntington's disease is reduced. It is also known that as individuals age, the length of the expanded trinucleotide pattern of CAG-polyglutamine repeats changes. It is further known that the level of estrogen in individuals decreases as individuals age. The data disclosed in the specification demonstrates at least two important aspects of the invention. Estradiol binds up the huntingtin polyglutamine protein, and that the affinity of the estradiol to bind to the

huntingtin protein depends directly on the length of the CAG repeat. As such, based on information known by those skilled in the art about the effect of binding the huntingtin polyglutamine protein, together with the disclosed aspects of the invention, the specification does teach a person skilled in the art that ensuring that an individual, known to carry the HD gene and known to have a CAG-polyglutamine repeat pattern greater than 38, should maintain a level of estrogen, normal for that individual, to optimize the binding affinity of estrogen to that individual's huntingtin polyglutamine proteins.

With respect to the Examiner's reference to Nausieda as teaching that oral contraceptives can induce chorea or involuntary movements, which happens to be one of many *symptoms* of HD, this certainly does not lead to the conclusion that estrogen should not be administered to individuals carrying the HD gene. As Bonelli, also cited by the Examiner, teaches, chorea is but one of many symptoms of HD. Chorea is a symptom of numerous diseases and oral contraceptives are known to have innumerable side effects, depending on an individual. Clearly, oral contraceptives do not cause chorea in all individuals who take oral contraceptives and Nausieda does not even suggest any connection with HD. The very first sentence of the Nausieda references states that "[c]horea is a rare complication of oral contraceptive medication... " In addition, Ott et al.'s conclusions, referred to by the Examiner as teaching that estrogen therapy does not attenuate cognitive declines in the elderly, only help to support the disclosure of the invention that administering estrogen sooner, rather than later, to an individual afflicted with HD, increases the binding affinity, and therefore the effect, of estrogen.

With respect to the cited teachings of Bonuccelli, all six of the individuals in

Bonuccelli's study were already exhibiting the disease, including chorea. In fact, the severity of the disease in five out of the six individuals was equal to or greater than 3 on a scale of 1-5. Bonucelli et al. did not study or measure the length of the patients' CAG repeat pattern and did not study the effect of estrogen relative to the length of the CAG repeat pattern. In contrast, one of the purposes of the subject invention is administer the estrogen before the symptomatic onset of the disease. The subject invention teaches that estrogen should be administered or otherwise regulated before the length of the CAG repeat pattern substantially decreases the binding affinity of estrogen and before most of an individual's natural reserves of hormones are depleted.

With respect to the Examiner's conclusion that estrogen and testosterone are not interchangeable for purposes of the claimed invention, the Applicant has amended claim 1 but has added claim 13. With regard to newly added claim 13, the binding affinity of estrogen and testosterone to the huntingtin protein, and their precursors would be quite similar if not identical. In fact, as shown in the cited Eckert reference, both testerone and progesterone are precursors to estradiol and are structurally similar.

Each of the Examiner's objections and rejections has been addressed. Accordingly, it is respectfully submitted that the application is in condition for allowance. Early and favorable action is requested.

If for any reason this Response is found to be incomplete, or if at any time it appears that a telephone conference with counsel would help advance prosecution, please telephone the undersigned in Worcester, Massachusetts at (508) 791-8500.

Respectfully submitted,

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